SUMMARY OF 96-C-0104 PROTOCOL

"A PILOT STUDY OF PACLITAXEL / CYCLOPHOSPHAMIDE AND HIGH DOSE MELPHALAN / ETOPOSIDE WITH AUTOLOGOUS PROGENITOR CELL TRANSPLANTATION FOR THE TREATMENT OF INFLAMMATORY BREAST CANCER"

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INTRODUCTION

Efforts to cure Inflammatory Breast Cancer have increasingly focused on dose intensive chemotherapies and the use of Taxanes. To date, the use of high-dose chemotherapy has not significantly changed survival for the majority of high-risk and metastatic patients. Most of these studies, however, have not so far demonstrated a statistically significant survival advantage for their transplant arm. However, in the setting of Inflammatory Breast Cancer, it appears clear from several phase II studies as well as from the International Bone Marrow Transplant Registry that patients who have received high-dose chemotherapy do benefit from it, showing a 3-4 year event-free survival in the 50-60% range (compared to the 25-30% after standard therapy). It is also clear that none of the ongoing randomized studies will ever provide a definitive answer for the small group of patients with Inflammatory Breast Cancer.

Our protocol (NCI 96-C-0104) has very encouraging results for patients with Inflammatory Breast Cancer, showing **70% Event-Free Survival with a median follow up of over 4 years**. These preliminary results were published in abstract form at the ASCO 2003 meeting. This protocol is part of a greater research project of immune reconstitution following chemotherapy. The better understanding of the mechanisms of immune reconstitution is leading our group to the design of studies of immune intervention following chemotherapy or Transplantation for various malignancies such as immune therapy or vaccine therapy.

The initial induction chemotherapy regimen is derived from an NCI dose escalation study of Paclitaxel (Taxol) and Cyclophosphamide (Cytoxan) in patients with metastatic breast cancer with progressive disease which showed over 70% response rate. It includes:

- Taxol (160 mg / m^2 continuous infusion over 72 hours) and three daily doses of Cytoxan (900 mg / m^2).
- Peripheral stem cell collection after the second cycle.
- Patients who have no evidence of disease (at entry on protocol) receive three cycles;
- Patients with clinical disease continue on this combination until maximum response (max. 9 cycles).
- Disease response is then re-evaluated every other cycle.
- The protocol requires that this chemotherapy be given at the NIH Clinical Center.

Any patient who has not previously received any anthracycline-containing regimen will then receive four cycles of Adriamycin / Cytoxan (AC) at standard doses which can be given by the referring physician. AC may also be given prior to the Taxol / Cytoxan combination without resulting in ineligibility as long as patients have not failed that regimen. Patients may or may not have undergone definitive surgery prior to entry on study. Patients may have received neo-adjuvant chemotherapy.

The transplant conditioning regimen consists of total doses of Melphalan 160 mg / m^2 and Etoposide 1800 mg / m^2 given over three days. Patients are usually discharged from the hospital from days 12 to 15. They are followed once a week for one month. This follow up can take place at the referring physician's office with weekly lab data faxed to NCI. Radiation therapy to the primary site is started 4 to 6 weeks after the high-dose therapy / transplant phase (given either at the NCI Clinical Center or locally). Patients undergo re-evaluation of their disease 6 weeks post transplantation and subsequently, every 6 months for 2 years. They are followed every 3 months at the Clinical Center for 2 years, then yearly thereafter.

ELIGIBILITY CRITERIA

- Histologically confirmed diagnosis of infiltrating carcinoma of the breast, stage III B Inflammatory Breast Carcinoma or clinical diagnosis of IBC
- Patients may have received (but not failed) prior induction / adjuvant therapy outside NCI
- Karnofsky performance status of > 70% (ECOG 0 or 1)
- Ejection fraction by MUGA or 2-D echocardiogram of > 45%
- Creatinine clearance of > 60 cc/mm^3
- AST and ALT < 3x upper limit of normal
- Bilirubin < 1.5 (except in cases of Gilbert's disease)
- ANC > l000/mm^3
- Platelet count > 90,000
- DLCO > 50%
- No history of medical or psychiatric disease which would preclude safe treatment in the view of the principal investigator
- No history of abnormal bleeding tendency or predisposition to repeated infections
- Patients must be able to give informed consent

NCI (96-C-0104): Paclitaxel / Cyclophosphamide and High Dose Melphalan / Etoposide with Autologous Progenitor Cell Transplantation for Inflammatory Breast Cancer